PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Marina Konopleva *et al.*	Group Art Unit: 1635
Serial No.: 09/998,009	Examiner: J. Anderson
Filed: November 28, 2001	Atty. Dkt. No.: UTSC:652US/SLH
For: CDDO-COMPOUNDS AND COMBINATION THERAPIES THEREOF	

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this declaration is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

September 4, 2007
Date

Steven L. Highlander

DECLARATION OF MICHAEL ANDREEFF UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

I, Michael Andreeff, do declare that:

1. I am the Michael Andreef named as an inventor on the above-captioned application. I am a citizen of Germany and reside at 2715 Pemberton Dr., Houston, TX. I currently hold the position of Professor of Medicine and Internist, Paul and Mary Haas Chair in Genetics, and Chief, Section of Molecular Hematology and Therapy at University of Texas M.D. Anderson Cancer Center in Houston TX.

2. I read the most recent official action regarding the above-captioned application, date April 4, 2007, and I understand the examiner to argue that the pending claims, drawn to combination cancer therapies using CDDO-me and another cancer therapy, should be limited to the treatment of only leukemia cells and should not include any chemotherapeutic agent. I must respectfully disagree with that position for the following reasons.

3. First, it is by now well-established that the anti-cancer effects observed with CDDO and related compounds, such as CDDO-me, are not limited to leukemia cells. For example, a numerous publications have been published that establish that these synthetic triterpenoids have activity against a wide range of cancers that form solid tumors, including breast, colon, pancreatic and ovarian cancers, thyroid carcinoma and metastatic melanoma:

1. Konopleva M, Lapillonne H, Clay CE, McQueen T, Studeny M, Madden T, Sporn M, Andreeff M: Activation of nuclear transcription factor PPARγ by the novel triterpenoid CDDO as targeted therapy in breast cancer. Keystone Symposium, #539, 2002.
2. Lapillonne H, Konopleva M, Tsao T, Gold D, McQueen T, Sutherland RL, Madden T, Andreeff M: Activation of peroxisome proliferator-activated receptor-γ by a novel synthetic triterpenoid 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic acid induces growth arrest and apoptosis in breast cancer cells. Cancer Res 63:5926-5939, 2003.
3. Konopleva M, Lapillonne H, Shi Y-X, McQueen T, Tsao T, Gold D, Johansen M-J, Madden T, Andreeff M: Synthetic triterpenoid CDDO as a novel therapy for resistant breast cancer. Proc. AACR, Vol. 44, March 2003.
4. Zhang W, Shi Y-X, McQueen T, Hung M-C, Madden T, Sporn M, Andreeff M, Konopleva M: Synthetic triterpenoid CDDO as effective therapy for HER2-expressing resistant breast cancer. Proc. AACR, #3799, 2004.
5. Melichar B, Konopleva M, Hu W, Melicharova K, Andreeff M, Freedman RS: Growth-inhibitory effect of a novel synthetic triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, on ovarian carcinoma cell lines not dependent on peroxisome proliferator-activated receptor-γ expression. Gynecologic Oncol 93:149-154, 2004.
6. Chintharlapalli S, Papineni S, Konopleva M, Andreeff M, Samudio I, Safe S. 2-cyano-3, 12-dioxoolean-1,9-dien-28-oic acid (CDDO) and related compounds inhibit growth of colon cancer cells through peroxisome proliferators-activated receptor γ-dependent and -independent pathways. Mol Pharmacol 68:119-128, 2005.

7. Samudio I, Konopleva M, Hail Jr N, Shi Y-X, McQueen T, Hsu T, Evans R, Honda T, Gribble GW, Sporn M, Gilbert HF, Safe S, Andreeff M: 2-cyano-3,12 dioxooleana-1,9 diene-28-imidazolide (CDDO-Im) directly targets mitochondrial glutathione to induce apoptosis in pancreatic cancer. J Biol Chem 280:36273-36282, 2005.
8. Konopleva M, Zhang W, Shi Y-X, McQueen T, Tsao T, Abdelrahim M, Munsell MF, Johansen M, Yu D, Madden T, Safe SH, Hung M-C, Andreeff M. Synthetic triterpenoid CDDO induces growth arrest in HER2-overexpressing breast cancer cells. Mol Cancer Ther 5:317-328, 2006.
9. Ling X, Konopleva M, Zeng Z, Ruvolo V, Stephens LC, Schober W, McQueen T, Dietrich M, Madden TL, Andreeff M. The novel triterpenoid C-28 methyl ester of 2-cyano-3,12-dioxoolen-1, 9-dien-28-oic acid inhibits metastatic murine breast tumor growth through inactivation of signal transducers and activators of transcription 3 signaling. Cancer Res 67:4210-4218, 2007.
10. Dezube B, Kurzrock R, Eder J, Supko J, Meyer J, Camacho L, Andreeff M, Konopleva M, Lescale-Matys L, Hong D: Interim results of a phase I trail with a novel orally administered synthetic triterpenoid RTA 402 (CDDO-Me) in patients with solid tumors and lymphoid malignancies. Am. Soc. Clin. Oncol. Meeting , Vol. 25 (supp), 14101, June 20, 2007.

As such, those of skill in the art would believe that when used in either mono- or combined therapies, CDDO and related compounds would be effective at treating solid tumors generally.

4. Second, it is also well-established that CDDO and related compounds can potentiate the anti-cancer activity of numerous different cancer therapies. For example, papers and abstracts reporting the combined effects of BH3 inhibitors, TRAIL and TRAIL receptor antagonists, TNF, 5-FU, taxol and doxorubicin have been published:

11. Konopleva M, Elstner E, McQueen T, Tsao T, Estrov Z, Koeffler HP, Sporn M, Andreeff M: PPARγ nuclear receptors as a novel therapeutic target in AML. Proc. AACR, Vol. 42, March, 2001.
12. Suh W-S, Shinichi S, Kim Y, Andreeff M, Sporn M, Suh, N, Reed J: Triterpenoids CDDO and CDDO-Me down-Regulate FLIP expression and sensitize cells to TRAIL-induced apoptosis. Am. Soc. Hematol. 43rd Annual Meeting and Exposition, December, 2001.
13. Konopleva M, Lapillonne H, Lee R-M, Wang R-Y, Tsao T, McQueen T, Andreeff M: PPARγ ligand CDDO induces apoptosis in leukemias via multiple apoptosis pathways. Am. Soc. Hematol. 44th Annual Meeting, December 2002.
14. Suh W-S, Kim YS, Schimmer AD, Kitada S, Minden M, Andreeff M, Suh N, Sporn M, Reed JC: Synthetic triterpenoids activate a pathway for apoptosis in

AML cells involving downregulation of FLIP and sensitization to TRAIL. Leukemia 17:2122-2129, 2003.

15. Shishodia S, Konopleva M, Andreeff M, Aggarwal BH: A synthetic triterpenoid methyl-2-cyano-3,12-dioxooleana-1,9-dien-280oate (CDDO-Me) inhibits IκBα kinase and enhances apoptosis induced by TNF and chemotherapeutic agents through downregulation of expression of NF-κB-regulated gene products in human leukemic cells. Clin Cancer Res 12:1828-1838, 2006.

16. Samudio I, Contractor R, Konopleva M, Andreeff M: The novel triterpenoid CDDOme potently synergizes with inhibition of bcl-2 function to induce apoptosis in AML via disruption of intracellular redox homeostasis, AACR, 96th Annual Meeting, April, 2005.

As such, those of skill in the art would also believe that a wide variety of combined therapies utilizing CDDO and related compounds would be effective at treating cancers.

5. Third, recent studies have demonstrated the efficacy of using CDDO and related compounds, including CDDO-Me, in combination with other anti-cancer therapies, for the treatment of solid tumors. For example

17. Andreeff M, Samudio I, Meyer C, Ling X, Shi Y-X, McQueen T, Dietrich M, Abbruzzese J, Kantarjian H, Konopleva M. Molecular mechanisms of CDDO-Me (RTA 402): antitumor effects and synergistic interactions with chemotherapy (personal communication,2006)

describe the successful results of combining CDDO-Me with gemcitabine in a murine orthotopic pancreatic model. Other positive pre-clinical data have been generated by my laboratory combining CDDO-Me with TRAIL receptor antagonists (NSCLC) and doxrubicin (NSCLC, breast cancer, pancreatic cancer). Finally, based on our preclinical work, the licensee of the present application, Reata Pharmaceuticals, is conducting a phase I clinical trial combining CDDO-Me with gemcitabine in the treatment of Stage IV pancreatic cancer, and positive responses have been observed (3/3 responses including one complete response (personal communication, Dr. C. Meyer, Reata Pharmaceuticals). This most unusual early result seems to

strongly support our preclinical findings that CDDO-derivatives can enhance chemotherapy effects in solid tumors.

6. Collectively, these findings clearly establish that CDDO and related compounds like CDDO-Me can treat a wide variety of cancers, either alone or in combination with a wide variety of anti-cancer therapies.

7. I declare that all statements made herein of my own knowledge are true, and that all statements of my own belief are believed to be true, and further that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

August 30, 2007

Date

Dr. Michael Andreeff